EXHIBIT F

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MEDLINE(R)

08263708 PMID: 2574310
Single domain antibodies.

Lancet (ENGLAND) Dec 9 1989 , 2 (8676) p1370-1 , ISSN: 0140-6736--
Print Journal Code: 2985213R
Publishing Model Print
Document type: Editorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

08461604 PMID: 2188691
Single domain antibodies.

Dick H M
Ninewells Hospital and Medical School, Dundee.

BMJ (Clinical research ed.) (ENGLAND) Apr 14 1990 , 300 (6730) p659-60
, ISSN: 0959-8138--Print Journal Code: 8900488
Publishing Model Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

09070540 · PMID: 1778186
Antibody engineering: an overview.

O'Kennedy R; Roben P
School of Biological Sciences, Dublin City University, Ireland.
Essays in biochemistry (ENGLAND) 1991 , 26 p59-75 , ISSN: 0071-1365--
Print Journal Code: 0043306
Publishing Model Print
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
We can now isolate and manipulate antibody genes. Mouse antibodies can be humanized, resulting in chimaeric or reshaped antibodies. Antibody engineering is useful in large scale production of antibodies, in production of active antibody fragments, bifunctional, single -domain and catalytic antibodies, and has lead to the production of novel expression systems useful in many other areas. It allows production of new antibody conjugates, e.g. antibody-toxin or antibody-enzyme linked proteins. Engineered antibodies have many potential applications e.g. imaging, therapy and biosensors.

09410309 PMID: 1427991
Rabbit single domain antibodies specific to protein C expressed in prokaryotes.

Suter M; Blaser K; Aeby P; Crameri R
Schweizerisches Institut fur Allergie- und Asthmaforschung, Davos, Switzerland.
Immunology letters (NETHERLANDS) Jun 1992 , 33 (1) p53-9 , ISSN: 0165-2478--Print Journal Code: 7910006
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
VDJ genes were amplified by the polymerase chain reaction from mRNA isolated from peripheral blood B cells of rabbits immunized with protein C. The amplified genes were cloned into a lambda phage expression vector and packaged. A library of 6 x 10(5) recombinant phages was screened with labelled protein C and 30 positive clones were found. Three of them were plaque purified and the affinity of the single domain antibodies to the antigen determined to be 10(6)-10(7) l M-1. The data indicate the feasibility of generating single domain antibody, specific to protein antigen, from rabbit.

10705954 PMID: 8536374
Molecular characteristics of anti-self antibody fragments against neutrophil cytoplasmic antigens from human V gene phage display libraries.

Finnern R; Bye J M; Dolman K M; Zhao M H; Short A; Marks J D; Lockwood M C; Ouwehand W H
University of Cambridge, Division of Transfusion Medicine, UK.
Clinical and experimental immunology (ENGLAND) Dec 1995 , 102 (3) p566-74 , ISSN: 0009-9104--Print Journal Code: 0057202
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Recently it has been demonstrated that human antibody fragments with binding activities against self antigens can be isolated from repertoires of rearranged V genes from non-immunized humans. We have applied phage display technology to study the B cell repertoire for antibody activity against neutrophil cytoplasmic antigens. These antibodies may play an important role in Wegener's granulomatosis (WG) and related forms of vasculitides. Autoantibodies in patients with WG are directed against proteinase 3. The immunodominant antigen in other forms of vasculitis is myeloperoxidase, but the B cell response can also be directed against other neutrophil enzymes, e.g. lysozyme, human neutrophil elastase, lactoferrin and cathepsin G. We show here that anti-self reactivity against neutrophil cytoplasmic antigens can be detected in the rearranged V gene repertoire of healthy individuals and that the reactivity can be directed against structural related epitopes which are present on different neutrophil cytoplasmic antigens. The scFv with binding activities were sequenced and the V gene usage, the level of somatic mutations and the immunoserological characteristics of the antibody fragments are discussed. Further evidence is presented that antibody fragments consisting only of a heavy chain variable domain can recognize neutrophil cytoplasmic antigens in a specific manner. These single-domain antibody fragments were used in experiments designed to establish the relative role of the light chain variable domains in antigen binding.

12456030 PMID: 10395823
An antibody single-domain phage display library of a native heavy chain variable region: isolation of functional single-domain VH molecules with a unique interface.

Reiter Y; Schuck P; Boyd L F; Plaksin D
Faculty of Biology, Technion-Israel Institute of Technology, Technion City, Haifa, 32000, Israel.
Journal of molecular biology (ENGLAND) Jul 16 1999 , 290 (3) p685-98 ,
ISSN: 0022-2836--Print Journal Code: 2985088R
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
To develop very small antibody-derived recognition units for experimental, medical, and drug design purposes, a heavy chain variable region (VH) single-domain phage-display library was designed and constructed. The scaffold that was used for library construction was a native sequence of a monoclonal antibody with a unique VH/VL interface. There was no need to modify any residues in the VL interface to avoid non-specific binding of VH domain. The library repertoire, consisting of 4x10(8)independent clones, was generated by the randomization of nine amino acid residues in complementary determining region 3. The library was screened by binding to protein antigens, and individual clones were isolated. The VH genes encoding for specific binding clones were rescued and large amounts of soluble and stable single-domain VH protein were made from insoluble inclusion bodies by in vitro refolding and purification. Biochemical and biophysical characterization of the VH protein revealed a highly specific, correctly folded, and stable monomeric molecule. Binding studies demonstrated an affinity of 20 nM. The properties of these molecules make them attractive for clinical, industrial, and research applications, as well as a step toward improvement in the design of small molecules that are based on the hypervariable loops of antibodies. Copyright 1999 Academic Press.